Q&A Graham Serjeant

Healthy progress

Physician Graham Serjeant reflects on how Jamaica's inhabitants have helped to advance our understanding of sickle-cell disease.

How have you been involved in sickle-cell disease research?

I moved to Jamaica 48 years ago, initially to develop services for patients with sickle-cell disease and to run the Medical Research Council Laboratories (Sickle Cell Unit) at the University of the West Indies in Kingston. I retired from that post about 15 years ago and have been working with a local charity called Sickle Cell Trust (Jamaica), where one of our most important projects — the Manchester project — focuses on prevention. Besides Jamaica, I have also worked on sickle-cell disease in Brazil, Saudi Arabia, India and a number of countries in Africa.

What does the Manchester project hope to achieve?

The long-term control and management of sickle-cell disease has to come in the form of prevention. Everyone has the right to knowledge of their haemoglobin genotype and to its significance (see page S2). They would then be empowered to make informed decisions.

The Manchester project seeks to inform a group of intelligent and motivated senior-school students of their haemoglobin genotype, then observe whether that knowledge influences their reproductive decisions and results in a significant reduction in

the number of babies born with sickle-cell disease. With support from the Jamaican ministries of health and education, we offered free, voluntary testing for haemoglobin genotype to students mostly aged 15–19 over a period of six years. We screened more than 16,000 students, almost 15% of whom carried abnormal genes. Every student received a laminated card, like a credit card, with their personal information and their genotype. Students with an abnormal genotype received additional information and counselling.

The next phase involved setting up newborn screening for south-central and western Jamaica — areas where the students were most likely to have their babies. The screening covers approximately 15,000 babies a year and so far, around 1,700 babies have been born to our informed cohort. The project appeared to be progressing well, until two mothers gave birth to babies with sickle-cell anaemia (who inherited a copy of the sickle-cell variant of the haemoglobin gene from both parents) within a period of two weeks. So far, of 845 females with the sickle-cell trait, four babies have been born with sickle-cell anaemia in 163 first pregnancies, which is close to the expected outcome had there been no intervention.

Have similar interventions been attempted in the past?

A smaller intervention known as the Orchomenos project was conducted in Greece between 1966 and 1970, but the results were not very encouraging. Four couples, in each of which both partners had the sickle-cell trait, had married. Two couples married with full knowledge of their genotypes and the related risks, and the other two had hidden their genotypes from their partners. But we have to persevere. By preventing as many cases as possible, we can ease the burden of providing clinical care for the patients that continue to be born.

How big is the current burden of sickle-cell disease?

Diarrhoea, infections and malaria may cause more deaths than sickle-cell disease, but as we begin to control these and other conditions, sickle cell is going to emerge as an increasingly larger problem. Not only are the numbers daunting — a quarter of a million babies are born with sickle-cell anaemia every year in sub-Saharan Africa alone — but once you have the disease, the problems may be life-long and require good monitoring and clinical care.

Has the global public-health response been sufficient?

In the past five years, there has been growing recognition of the importance of the disease, and the realization that much can be done to prevent many of the associated health problems. Instead of sitting back helplessly and saying, "This is a genetic disease and we cannot

cure it", the truth is that you actually don't have to cure it. If people can survive to the age of 80, as some of our patients in Jamaica do, then that is a disease that we can live with. The National Sickle Cell Anemia Control Act, passed in 1972 in the United States, was a major stimulus for raising awareness of the need for education, counselling and population screening.

But lack of political will continues to significantly impede progress. Faced with the multitude of clinical problems, some health-care personnel in Africa may say: "So, the children die? Well, thank God for that!" From their perspective, sickle cell shrinks into the background compared to the more immediate and overwhelming

"Once you have sickle-cell disease, the problems may be life-long and require good monitoring and clinical care."

problems of HIV, malnutrition, infections, septicaemia and Ebola, among others. But in the long term, they are going to be left with sickle-cell disease, and services have to be developed. There have been some positive developments with the establishment of dedicated centres in Lagos, Nigeria and Kumasi in Ghana, but it is going to be a long haul.

Meanwhile, India has made great progress. In the past 15 years, three states have established state-managed sickle-cell control programmes. They are: Gujarat, Maharashtra and Chhattisgarh, where sickle-cell disease is endemic among the scheduled castes and scheduled tribes (historically marginalized and socioeconomically disadvantaged groups identified by the Indian Constitution for special consideration). I am not aware of any African country that has done that.

How have interventions in recent years improved patients' quality of life?

We can now diagnose the disease at birth; the technology is simple and the population is accessible. Major causes of morbidity and mortality — especially in the second six months of life — such as pneumococcal septicaemia, acute splenic sequestration, acute chest syndrome, and even stroke can be prevented by simple interventions.

The painful crises, which become a problem in adolescence, are more difficult to manage. But we have models of care that work well in our Jamaican population, which involve improving the capacity of patients to cope with the pain by talking them through it. This may not be possible in societies in which doctors have limited time or feel obliged to do more for their patients. In such situations, a shot of morphine or the preventative drug hydroxyurea may be the solution, but not for our Jamaican patients in whom our alternative methods have worked,

Screening for the sickle-cell gene as part of the Manchester project, run by Sickle Cell Trust (Jamaica).

especially given the relatively high cost of hydroxyurea and concerns about the potential side effects. A crucial element of the success in Jamaica has been the provision of diagnostic services in dedicated sickle-cell centres that are staffed with experts who are familiar with the disease and their patients.

The median survival for sickle-cell anaemia is less than five years in sub-Saharan Africa (although formal survival estimates are not available), but in Jamaica it is 55 years. This is still about 20 years shorter than the general population, but our early childhood interventions, which we began implementing in the early 1980s, have yet to feed through to be reflected in overall survival rates.

What has been the most important thing that you have learned about the disease?

When I first came to Jamaica in 1966, our sickle-cell clinic at the University Hospital of the West Indies was attended by patients with sickle-cell anaemia who were between 30 and 40 years old — an observation at total variance with the traditional descriptions of the disease, which referred to it as almost always causing death in childhood. One possible hypothesis was that these traditional descriptions were based on a highly selected, symptomatic group of patients available to the doctors writing on sickle-cell disease. We tested this hypothesis with support from the Wellcome Trust in London by driving all over Jamaica in a mobile clinical unit to locate patients who had been known to the University Hospital but had not been seen for ten years. We found more than half of the patients, all of whom said that their symptoms had improved with age, so they had no need to waste their time seeing a doctor at the hospital.

That was a big surprise, and we realized that once you can get out into the community, you get to see the other side of the disease. It was a supreme example of the value of Jamaica

as a clinical laboratory, being an island with a strong extended-family system and many patients, 5,500 of whom were under regular observation at the sickle-cell clinic.

These early observations led to the Jamaican Cohort Study in 1973, when the Sickle Cell Unit began screening 100,000 consecutive, non-operative births at Victoria Jubilee Hospital in Kingston, and detected 550 children with different genotypes of sickle cell who are being followed for life. The cohort study has helped to define the true natural history of sickle-cell disease and develop cost-effective interventions to improve the outcome of the disease.

Can the wide variation in disease severity be explained by genetics?

One of the classic methods for distinguishing genetic from environmental factors in disease is studies of identical twins. We identified nine pairs of identical twins in Jamaica, of whom six had sickle-cell anaemia. Analysis showed that identical twins were similar in terms of haematology and growth, but discordant in virtually all other clinical features. Even though these twins were genetically identical, their experience of the disease was very different. Genetics accounted for only a small portion of the variability in the disease.

Interestingly, that was not a message that people wanted to hear in the post-genome era, and we faced considerable difficulty in getting those results published. But to me, the results were hopeful because we cannot change someone's genes but we can change his or her environment. There is also a huge psychological component to consider, such as the role of stress in inducing serious complications. I have seen people die in a painful crisis during their university exams. The tremendous clinical variability of the disease still remains one of the biggest unknowns. ■

INTERVIEW BY SMRITI MALLAPATY